Dementia is a Latin-derived word that stems from ‘demens’ meaning to be ‘out of one’s mind’. The term was first used in ancient Rome and can be found in Roman medical texts and in the philosophical works of Cicero. The medical use of this term has evolved through the centuries and in 1906, AD, the most common form of dementia, was described for the first time by the German psychiatrist and neuropathologist, Alois Alzheimer, and later named after him.

Dementia is a progressive neurological and degenerative syndrome affecting an estimated 35.6 million people worldwide in 2010, with numbers expected to double every 20 years to over 100 million by 2050.1 It is characterised by deterioration in patients’ cognitive function, involving memory loss, language impairment and disorientation as well as impairment in their ability to carry out activities of daily living (ADL).2 In addition to these predominant features, more than 80% of patients will also display a variety of accompanying behavioural and psychological symptoms including psychosis, agitation, aggression, mood disorders, wandering and sexual disinhibition.3,4

Several different types of dementia have been described over the years and are classified according to the various disease processes affecting the brain’s functioning. AD accounts for about 60% of all dementia cases; vascular dementia and dementia with Lewy bodies (DLB) are responsible for the majority of other cases.2 It is quite common for AD and vascular dementia to co-exist in the same patient and they are often difficult to separate clinically.

**Pathophysiology**
The classic pathological features in AD include the presence of senile plaques, which develop between neurons in the brain and neurofibrillary tangles, which develop within neurons. These microscopic changes are believed to be an integral part of the cause, development and course of the illness.5

Senile plaques comprising of insoluble β-amyloid polypeptides appear to form as a result of disorders in processing β-amyloid and its precursor protein, amyloid precursor protein (APP). One theory is that inflammation around the plaques destroys neighbouring neurones5 and leads to the formation of neurofibrillary tangles.

Healthy neurones have an internal support structure partly made up of structures called microtubules, which act like tracks, guiding nutrients and molecules from the body of the cell down along the axons. A protein called tau stabilises these microtubules.

In AD, tau is changed chemically and undergoes hyperphosphorylation. Neurofibrillary tangles consist partly of hyperphosphorylated tau, which then links together to form filaments, the density of

---

**Figure 1.** Production of acetylcholine (ACh) in the presynaptic neurone and its breakdown by acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). ChAT, choline acetyltransferase. Reproduced with permission from: Scarpini E, Scheltens P, Feldman H. Treatment of Alzheimer’s disease: current status and new perspectives. Lancet Neurol 2003;2:539-47.28

---
which is thought to be directly related to the severity of dementia.

The resulting effect of these neurofibrillary tangles is to compromise microtubular function, with the eventual destruction of the neurone. These abnormal processes affecting cholinergic neurones lead to a decline in levels of acetylcholine (ACh) within synapses (see Figure 1).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Donepezil (Aricept®) (Pfizer, Eisai)</th>
<th>Rivastigmine (Exelon®) (Novartis)</th>
<th>Galantamine (Reminyl®) (Shire/Janssen-Cilag)</th>
<th>Memantine (Exiba®) (Lundbeck)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary mechanism</td>
<td>AChE-I (selective + reversible)</td>
<td>AChE-I (pseudo-irreversible)</td>
<td>AChE-I (selective + reversible)</td>
<td>NMDA receptor antagonist</td>
</tr>
<tr>
<td>Other mechanism</td>
<td>None</td>
<td>BuChE-I</td>
<td>Nicotine modulator</td>
<td>5-HT3 receptor antagonist</td>
</tr>
<tr>
<td>Starting dose</td>
<td>5 mg daily</td>
<td>1.5 mg bd (oral) (or 4.6mg/24 hrs patch)</td>
<td>4 mg bd (or 8 mg XL daily)</td>
<td>5 mg daily</td>
</tr>
<tr>
<td>Usual treatment dose (max dose)</td>
<td>10 mg daily</td>
<td>6 mg bd (oral) or 9.5mg /24 hours patch</td>
<td>12 mg bd (or 24 mg XL daily)</td>
<td>20mg daily or (10mg bd)</td>
</tr>
<tr>
<td>Recommended minimum interval between dose increases</td>
<td>4 weeks (increase by 5mg daily)</td>
<td>2 weeks for oral (increase by 1.5mg twice a day)</td>
<td>4 weeks (increase by 4mg twice a day or 8mg XL daily)</td>
<td>1 week (increase by 5mg daily)</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>Diarrhoea*, nausea*, headache*, common cold, anorexia, hallucinations, agitation, aggressive behaviour, abnormal dreams and nightmares, syncope, dizziness, insomnia, vomiting, abdominal disturbance, rash, pruritus, muscle cramps, urinary incontinence, fatigue, pain</td>
<td>Anorexia*, dizziness* nausea* vomiting* diarrhoea*, agitation, confusion, anxiety, headache, somnolence, tremor, abdominal pain and dyspepsia, sweating fatigue and asthenia, malaise, weight loss</td>
<td>Nausea*, vomiting*, decreased appetite, anorexia; hallucination, depression, syncope, dizziness; tremor, headache, somnolence, lethargy, bradycardia, hypertension, abdominal pain and discomfort, diarrhoea, dyspepsia, sweating, muscle spasms, fatigue, asthenia, malaise, weight loss</td>
<td>Drug hypersensitivity, somnolence, dizziness, balance disorders, hypertension, dyspnoea, constipation, elevated liver function test, headache</td>
</tr>
<tr>
<td>Management of adverse effects</td>
<td>Stop treatment if the following adverse effects occur: bradycardia, gastrointestinal ulceration</td>
<td>Reduce dose or discontinue if intolerable if the following adverse effects occur: nausea, vomiting, diarrhoea, muscle cramps, insomnia, fatigue</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Pharmacology**

**Acetylcholinesterase inhibitors (AChEIs)**

The cholinergic hypothesis of AD was put forward following the observation that cognitive deterioration results from a progressive loss of cholinergic neurones and a decrease in levels of acetylcholine in the brain. Thus the mainstay of treatment for AD to date has been the use of agents that inhibit the degradation of acetylcholine within the synapse and so enhance cholinergic neurotransmission. Tacrine was the first AChEI to be approved for the treatment of mild-to-moderate AD over 15 years ago. However, it is no longer prescribed because of its poor tolerability and risk of hepatotoxicity.

In the UK, there are three second-generation AChEIs licensed for the treatment of mild-to-moderate dementia in AD: donepezil, rivastigmine and galantamine. These agents differ in their pharmacological actions, particularly in relation to enzyme specificity. Donepezil selectively inhibits AChE, rivastigmine inhibits both AChE and butyrylcholinesterase (BuChE) and galantamine selectively inhibits AChE but also has activity as an allosteric modulator of nicotinic acetylcholine receptors (nAChRs). Because a decrease in the expression and activity of nicotinic acetylcholine receptors largely contributes to the overall reduction in central cholinergic neurotransmission, this last mechanism is also considered important in the treatment of AD. See Table 1 for characteristics of AChEIs.

**Memantine**

Memantine is licensed in the UK for AD but, unlike the AChEIs, it is licensed in moderately severe to severe disease. It has a separate mode of action, acting as an antagonist at N-methyl-D-aspartate (NMDA) receptors, an action believed to be neuroprotective and disease-modifying.

Excitotoxicity occurs when there is excessive exposure to the neurotransmitter glutamate or over-stimulation of glutamate receptors, resulting in injury or death of neurones. This neuronal death is partly mediated by overactivation of NMDA-type glutamate receptors resulting in an excessive influx of calcium ions (Ca2+) through the receptors’ associated ion channel. However, because physiological NMDA receptor activity is essential for normal neuronal function, the total block of NMDA receptor activity would be clinically unacceptable. However, the adamantane derivative, memantine selectively blocks excessive NMDA receptor activity without disrupting normal activity. See Table 1 for characteristics of memantine.

- The three AChEIs donepezil, galantamine and rivastigmine are recommended for managing mild-to-moderate Alzheimer’s disease (AD). Memantine is recommended for managing moderate AD for people who are intolerant of or have a contraindication to AChEIs, or for managing severe AD.
- Carers’ views on the patient’s condition at baseline and follow-up should be sought.
- Patients who continue on the drug should be reviewed regularly using cognitive, global, functional and behavioural assessment. Treatment should be reviewed by an appropriate specialist team, unless there are locally agreed protocols for shared care.
- Therapy with AChEI should be initiated with a drug with the lowest acquisition cost. An alternative may be considered on the basis of adverse effects profile, concordance, medical co-morbidity and possibility of drug interactions.
- When assessing the severity of AD and the need for treatment, healthcare professionals should not rely solely on cognition scores in circumstances in which it would be inappropriate to do so, and should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the results. Any adjustments considered appropriate should be made.

**Table 2. Summary of NICE guidance on acetylcholinesterase inhibitors (AChEIs).**


---

**Evidence base supporting pharmacotherapy Alzheimer’s disease**

In recent years, the use of AChEIs has generated much controversy among scientists, consumers and non-statutory organisations. The debate is not over efficacy, since there is reasonable evidence for this, but rather about the magnitude of the benefit. Discussions also continue over what stage of the disease these agents should be withdrawn.

The National Institute for Health and Care Excellence (NICE) recommends treatment with AChEIs for mild-to-moderate AD. Memantine is recommended for severe AD or for moderate AD in people who are either intolerant of, or have a contraindication to AChEIs. NICE also specify that carers’ views on a patient’s condition should be sought at baseline and follow-up, and that patients who continue on the drug should be reviewed regularly using cognitive, global, functional and behavioural assessment. NICE defines severity of AD using Mini-Mental State Examination (MMSE) – mild (defined as MMSE 21-26), moderate (MMSE 10-20) and severe (MMSE <10). When assessing the severity of AD and the need for treatment, NICE recommends that healthcare professionals should not rely solely on cognition scores and that they should take into account any physical, sensory or learning disabilities or communication difficulties that could affect the results, with appropriate adjustments made where necessary.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Metabolism</th>
<th>Plasma levels increased by</th>
<th>Plasma levels decreased by</th>
<th>Pharmacodynamic interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil (Aricept®)</td>
<td>Substrate at 3A4 and 2D6</td>
<td>Ketoconazole, Itraconazole, Erythromycin, Quinidine, Fluoxetine</td>
<td>Rifampicin, Phenytoin, Carbamazepine, Alcohol</td>
<td>Antagonistic with anticholinergic drugs. Potential for synergistic activity with cholinomimetics such as neuro-muscular blocking agents (e.g. succinylcholine), cholinergic agonists and peripherally acting cholinesterase inhibitors eg neostigmine. Beta blockers, amiodarone or calcium channel blockers may have additive effects on cardiac conduction.</td>
</tr>
<tr>
<td>Rivastigmine (Exelon®)</td>
<td>Non-hepatic metabolism</td>
<td>Metabolic interactions appear unlikely</td>
<td>None known</td>
<td>Antagonistic effects with anticholinergic and additive effects cholinomimetic drugs, succinylcholine - type muscle relaxants, cholinergic agonists e.g. bethanechol or peripherally acting cholinesterase inhibitors e.g. neostigmine. Synergistic effects on cardiac conduction with beta blockers, amiodarone, calcium channel blockers.</td>
</tr>
<tr>
<td>Galantamine] (Reminy®)</td>
<td>Substrate at 3A4 and 2D6</td>
<td>Ketoconazole, Erythromycin, Ritonavir, Quinidine, Paroxetine, Fluoxetine, Fluvoxamine, Amitriptyline</td>
<td>None known</td>
<td>Antagonistic effects with anticholinergic and additive effects cholinomimetics, succinylcholine - type muscle relaxants, cholinergic agonists and peripherally acting cholinesterase inhibitors eg neostigmine. Possible interaction with agents that significantly reduce heart rate e.g. digoxin, β blockers, certain calcium-channel blockers and amiodarone. Caution with agents that can cause torsades de pointes (manufacturers recommend ECG in such cases).</td>
</tr>
<tr>
<td>Memantine (Exiba®)</td>
<td>Primarily non-hepatic metabolism, Renally eliminated</td>
<td>Cimetidine, Ranitidine, Procainamide, Quinidine, Quinine, Nicotine, Isolated cases of INR increases reported with concomitant warfarin (close monitoring of prothrombin time or INR advisable) Drugs that alkalize urine (PH ~8) may reduce renal elimination of memantine eg carbonic anhydrase inhibitors, sodium bicarbonate</td>
<td>None known (Possibility of reduced serum level of hydrochlorothiazide when co administered with memantine)</td>
<td>Effects of L-dopa, dopaminergic agonists and anticholinergics may be enhanced Effects of barbiturates and neuroleptics may be reduced Avoid concomitant use with amantadine, ketamine and dextromethorphan -risk of pharmacotoxic psychosis. One published case report on possible risk for phenytoin and memantine combination Dosage adjustment may be necessary for antispasmodic agents, dantrolene or baclofen when administered with memantine</td>
</tr>
</tbody>
</table>

Table 3. Drug-drug interactions between acetylcholinesterase inhibitors or memantine and other drugs. Taken from: Taylor D, Paton C, Kapur S. The Maudsley Prescribing Guidelines, 12th edn, 2015."
Cochrane reviews of AChEIs concluded that treatment for six months produced statistically significant improvements in cognitive function, and benefits were also noted on measures of ADL and behaviour, although none of these treatment effects were large.\textsuperscript{12} The Cochrane review for memantine concluded that it had a small beneficial, clinically detectable effect on cognitive function and functional decline at six months in moderate to severe AD.\textsuperscript{13} A meta-analysis found no significant differences between memantine and placebo on any outcome for patients with mild AD.\textsuperscript{14} Despite the slight variations in their modes of action, there remains no evidence to suggest that individual AChEIs differ in terms of efficacy.\textsuperscript{12} Direct comparisons between AChEIs have produced equivocal results with company-sponsored studies favouring the manufacturers’ own drugs.\textsuperscript{15} However, a large double-blind randomised-controlled trial that was included in the Cochrane review of AChEIs comparing donepezil with rivastigmine found no difference in improvement of cognitive function or behaviour at two years.\textsuperscript{16} The decision about when to stop treatment has led to much debate. Recent evidence suggests that continued use of AChEI therapy, even during the severe stages of the disease may be beneficial. A large multicentre study of community-dwelling patients with moderate or severe AD investigated the long-term effects of donepezil over 12 months compared with stopping donepezil after three months, switching to memantine or combining donepezil with memantine. Continued treatment with donepezil was associated with continued cognitive benefits and patients with a Mini Mental State (MMSE) score as low as 3 were still benefiting from treatment.\textsuperscript{17} Similarly, a meta-analysis evaluating the efficacy of the three AChEIs and memantine in relation to the severity of AD found that the efficacy of all drugs was independent of dementia severity in all domains. Results showed that patients in differing stages of AD retained the ability to respond to treatment with AChEIs and that medication effects were therefore substantially independent from disease severity.\textsuperscript{18} This suggests that patients should continue treatment with AChEIs for as long as possible, that there should not be a cut-off MMSE score where treatment is stopped automatically and that the severity of a patient’s illness should not preclude treatment with these drugs. Whilst AChEIs are not currently licensed in the UK for severe AD and NICE do not currently recommend their use for this stage of the illness, it is possible that their indication may be extended to severe AD in the near future in view of this latest evidence. Indeed, donepezil is already approved in the US for severe AD. When drug administration is interrupted, the benefits of AChEIs are rapidly lost\textsuperscript{19} and may not be fully regained on re-initiation.\textsuperscript{20} Poor tolerability with one agent does not rule out good tolerability with another.\textsuperscript{21} There is conflicting evidence for combining AChEIs with memantine. Whilst long-term observational studies found the combination to be associated with better cognitive outcomes and greater delays in time to nursing home admission compared with monotherapy or no treatment, a meta-analysis found that the benefits of combined therapy were not clinically significant.\textsuperscript{22} Also, a large multicenter study found that the efficacy of donepezil and of memantine did not differ significantly in the presence or absence of the other and that there were
<table>
<thead>
<tr>
<th>Agent(s)</th>
<th>Mechanism of action</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs Cyclo-oxygenase (COX-2) inhibitors</td>
<td>Anti-inflammatory: plaque-associated inflammation causes cellular damage</td>
<td>Results from RCTs were disappointing(^{32})</td>
</tr>
<tr>
<td>HMG-CoA reductase inhibitors (statins)(^{33})</td>
<td>Cholesterol depletion strongly inhibits β-amyloid secretion and amyloid precursor protein processing, although exact mechanism for this is not known</td>
<td>Cochrane review found insufficient evidence to recommend statins as analysis found no benefits on cognitive function(^{33})</td>
</tr>
<tr>
<td>Secretase inhibitors(^{34,35})</td>
<td>Secretase enzymes are involved in β-amyloid processing. β-amyloid is generated from amyloid precursor protein by β- and γ-secretases</td>
<td>Semagacestat (γ-secretase inhibitor)- interrupted at phase III (no efficacy and risk of skin cancer) Avagacestat (γ-secretase inhibitor) – phase II trial found worsening of cognitive function and risk of skin cancer β-secretase inhibitors – ongoing(^{27})</td>
</tr>
<tr>
<td>Metal chelators</td>
<td>Dissolve amyloid plaques Copper and zinc are implicated in the formation of amyloid plaques</td>
<td>More data on safety and efficacy are required</td>
</tr>
<tr>
<td>Immunisation (vaccine)</td>
<td>Production of β-amyloid antibodies Lowering of amyloid burden</td>
<td>Phase II of active immunisation vaccine suspended following cases of meningoencephalitis Passive immunization: Bapineuzumab – two large phase III trials failed to show improvement in cognition and caused serious vasogenic oedema in the brain Solanezumab – two large phase III trials failed to slow decline in cognitive and memory functions but may be effective in early stages of AD Gantenerumab and crenezumab are currently in phase II trials(^{27,32})</td>
</tr>
<tr>
<td>Antibiotics, eg tetracyclines, rifampicin</td>
<td>Reduce inflammatory cytokines Interfere with plaque development</td>
<td>More data on efficacy are required RCT for minocycline underway</td>
</tr>
<tr>
<td>Tau kinase inhibitors,(^{36}) eg lithium</td>
<td>Reduce tau hyperphosphorylation Prevention of tangles</td>
<td>Clinical evidence so far is promising but large scale clinical trials are still required to assess benefit(^{37})</td>
</tr>
<tr>
<td>Tau aggregation inhibitors(^{38})</td>
<td>Facilitate the proteolytic degradation of tau aggregates</td>
<td>TRX-0237 – Ongoing trial</td>
</tr>
<tr>
<td>Oestrogens</td>
<td>Possibly neurotrophic and enhances neurotransmission</td>
<td>Conflicting evidence showing both benefit and harm</td>
</tr>
<tr>
<td>Curcumin (extract of turmeric)(^{39})</td>
<td>Anti-inflammatory and anti-oxidant properties. May inhibit the formation of β-amyloid fibrils and induce dissociation of pre-formed ones</td>
<td>Clinical trials sponsored by the National Institutes of Health are underway</td>
</tr>
<tr>
<td>Dimebolin (Dimebon®, latrepirdine)(^{40})</td>
<td>Weak inhibitor of butirylycholinesterase and acetylcholinesterase. Also weakly blocks NMDA receptor signalling pathway</td>
<td>Trial results showed that dimebolin presented a good safety profile but failed to exert a significant beneficial effect over placebo, leading to discontinuation of its development for AD(^{41,42})</td>
</tr>
</tbody>
</table>

Table 4. Futures treatments for Alzheimer's disease and their mechanism of action\(^{28-31}\)
no significant benefits for the combination over donepezil alone.17 The combination does, however, appear to be well tolerated and may even result in reduced incidence of gastrointestinal (GI) adverse effects compared with an AChEI alone.23 (See Table 3 for interactions of AChEIs or memantine with other drugs). A variety of other agents have been used to treat AD, including Gingko biloba, vitamin E, folic acid, ginseng and omega-3, but their clinical benefit remains inconclusive.24

Other dementias
At present, AChEIs and memantine have not been approved for use in non-Alzheimer’s dementias. NICE does not recommend their use in vascular dementia (however, AChEIs can be considered in patients with DLB who have non-cognitive symptoms – see below). Cochrane reviews found that the evidence for AChEIs in vascular dementia was inconsistent and, although a meta-analysis of RCTs showed small benefits on cognition with AChEIs and memantine, these improvements were of uncertain clinical significance. There is currently insufficient evidence to support the use of these agents in vascular dementia.24

Behavioural and psychological symptoms of dementia (BPSD)
AChEIs may provide some benefit in the management of BPSD; however, their effect is only apparent after several weeks of treatment and trial evidence remains somewhat inconsistent. Similarly, although memantine continues to garner evidence for use in BPSD, its use is still controversial. 24

NICE recommends only considering the use of AChEIs for:

- People with DLB who have non-cognitive symptoms causing significant distress or leading to behaviour that challenges
- People with mild, moderate or severe AD who have non-cognitive symptoms and/or behaviour that challenges causing significant distress or potential harm to the individual if:
  - a non-pharmacological approach is inappropriate or ineffective
  - antipsychotic drugs are inappropriate or ineffective.

The use of antipsychotics in patients with dementia has led to much controversy as they are associated with an increased risk of cerebrovascular events and higher mortality in this patient group.25 Antipsychotics should be prescribed in dementia only if the benefits outweigh the potential risks, and regular reviews should be carried out.

Risperidone is the only drug approved in the UK for BPSD. It is indicated for short-term treatment (up to six weeks) of persistent aggression in patients with moderate-to-severe Alzheimer’s disease unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others. Other agents used in BPSD include antidepressants, mood stabilisers and benzodiazepines (for further information on the management of BPSD, see ‘Management of non-cognitive symptoms of dementia’, DTB 2014;52:114-8.)

Future treatments for dementia
The future of AD treatment is in disease modification, with the hope and expectation that this will translate into meaningful and significant clinical outcomes. Recently, several investigational drugs for the treatment of AD have failed in early clinical trials, either due to lack of efficacy or concerns over safety. Among these are two anti-amyloid monoclonal antibodies (solanezumab and bapineuzumab) and one γ-secretase inhibitor (semagacestat). These failures have raised the question as to whether patients recruited for inclusion in these trials had AD that was too far advanced to be helped by inhibiting further production or removal of existing β-amyloid plaques. It seems that the only way to tackle this issue is to recruit younger patients who have not yet developed AD, although this understandably raises ethical issues.27 Table 4 summarises the agents that are currently in development. Figure 2 illustrates the different stages involved in the formation of plaques and neurofibrillary tangles seen in AD. The stage at which each future treatment acts is highlighted.

Conclusion
The pharmacological management of AD is a challenging area for prescribers. AChEIs and memantine remain the only drugs approved for use in AD. Recent evidence suggests that patients should continue treatment with AChEIs for as long as possible as benefits can be seen even in the severe stages of the illness. The decision to stop treatment should be based on a holistic assessment of the patient.

Although some studies have looked at the use of AChEIs in other dementias and in BPSD, there is currently no robust evidence for their effectiveness in these conditions, although NICE recommends considering their use in DLB, when other options are either ineffective or not appropriate. A number of treatments are being studied for the management of AD, although many are still in the initial stages of evaluation.
Declaration of interests

Professor Taylor has received payments for lectures and advisory boards from Eli Lilly, Lundbeck, BristolMyersSquibb, AstraZeneca, Sunovion and Otsuka.

Ms Bishara is Consultant Pharmacist for Mental Health of Older Adults and Dementia at The Maudsley Hospital, South London and the Maudsley NHS Foundation Trust, Dr Sauer is Consultant Psychiatrist and Clinical Director for Mental Health of Older Adults and Dementia Clinical Academic Group at The Maudsley Hospital, South London and the Maudsley NHS Foundation Trust and Professor Taylor is Director of Pharmacy at The Maudsley Hospital, South London and the Maudsley NHS Foundation Trust.

References